Remarks

The present invention relates to carrier solutions for the introduction and washout of vitrifiable concentrations of cryoprotectants in a cell, tissue, or organ. The present invention teaches the inclusion of mannitol and lactose in such solutions. In various embodiments, the solutions can contain one or more of dimethyl sulfoxide, formamide, ethylene glycol, acetol, polyglycerol, and a copolymer of vinyl alcohol and vinyl acetate as cryoprotectants. The solutions of the present invention are extraordinarily effective due to their surprising lack of toxicity and their surprising stability against ice formation. The solutions of the present invention minimize toxicity, cooling injury, and devitrification. The solutions are useful for the preservation of tissues and organs, for which rapid cooling and warming is difficult.

By the present communication, claims 4, 7, 20, 25, and 28 have been amended to better define the invention of the application. In addition, claims 16-18 and 23-24 are cancelled without prejudice to further prosecution and solely to obtain quick allowance of clearly allowable subject matter. Claims 1-4, 6-10, 13, 15, 19-22, and 25-32 are pending in the application after this amendment.

The Examiner rejects claims 7, 24-25, and 30 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to convey to one skilled in the art that the inventor, at the time of the application, had possession of the claimed invention. This rejection is respectfully traversed.

Contrary to the Examiner's assertion (Office Action mailed 11/5/2003, p. 2), claim 7 does not include new matter by the recitation of "sucrose" in the claim, as support for the inclusion of sucrose appears at p. 6, line 18 of the present specification.

The Examiner's assertion that claim 7 is allegedly not supported by the disclosure as filed with respect to the classification of polyglycerol, PVP, PVA, and a copolymer of vinyl alcohol and vinyl acetate as "impermeants" is respectfully submitted to be without merit. Each of the recited species are large molecules that are very well known in the art as impermeants. Nevertheless, solely in order to remove issues from the case and advance speedy prosecution, the claim has been amended to recite "polymers" instead of "impermeants."

The Examiner's rejection of claims 27-29 under 35 U.S.C. 112, second paragraph as allegedly being indefinite for the recitation of X1000, DMSO, and LM5 is respectfully traversed. X1000 is defined at page 8, in the legend to Table 2. X1000 is also described on page 1 as an "ice blocking" or antinucleating agent of the polyvinyl alcohol type, and is also defined precisely in the legend of Table 2. "DMSO" is defined as "dimethyl sulfoxide" in the legend of Table 3. "LM5" is defined in precise detail on page 12, lines 18-21. "LM5" is also described clearly in Example 1 as being a modification of RPS-2, with instructions provided on how to modify RPS-2 to make LM5. The composition of RPS-2 is known in the art and is also stated at page 12, lines 16-18, as well as being described in the Fahy and Ali reference provided on page 2, line 9. In view of this disclosure it is submitted that the claims are not indefinite. The Examiner is also referred to the response filed March 31, 2003, page 6-8 where the discussion of many of these terms in the specification was indicated.

The rejection of claims 1-2, 7, and 19 under 35 U.S.C. 102(b) as allegedly being anticipated by JP 1-106826 is respectfully traversed. It is pointed out that claim 1 is in the Jepson format, and therefore the preamble cannot be ignored as an element. The present claims recite carrier solutions for the introduction and washout of "vitrifiable" concentrations of cryoprotectants in a cell, tissue, or organ where the solution comprises mannitol and lactose in a solution. The instant reference discloses only a blood preserving solution containing a hemolysis inhibitor, and completely fails to disclose or suggest the combination of mannitol and lactose in such a solution. Rather, the reference merely presents these two compounds in a list of possibilities and does not suggest any advantages to be gained by making the claimed combination, nor does the reference suggest the combination. The reference fails even to suggest a carrier solution for the introduction and washout of vitrifiable concentrations of cryoprotectant.

Furthermore, the instant reference does not indicate that the disclosed solutions have any utility for the purpose recited in the claim. Furthermore, the reference makes no reference to the inhibition of ice-blocking activity by glucose and the ability of lactose and mannitol to overcome the inhibition of the ice blocking activity of X1000, as does the presently claimed invention (page 6, lines 10-12 of thespecification). Therefore, no suggestion is provided by the reference to make the asserted combination of ingredients and use the solution for the recited purpose. It appears that the Examiner has made this rejection based on a hindsight determination using the Applicant's disclosure as a blueprint. But the patent laws do not permit a rejection to be made on this basis. For all of these reasons, reconsideration and withdrawal of the rejection is respectfully requested.

The Examiner rejects claims 1-3, 10, 13, 15-16, 19, 22-26, 30-32 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,194,137 (Khirabadi). This rejection is respectfully traversed.

Establishment of a prima facie case of obviousness has 3 requirements: 1) there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill, to modify the reference or to combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. MPEP 2142; *In re Vaeck*, 947 F.2d 488; 20 USPQ2d 1438 (Fed. Cir. 1991).

As acknowledged by the Examiner, Khirabadi does not disclose that one combination of cryoprotectants over another combination provides better results (Office Action mailed 11/5/2003, p. 7). In spite of this acknowledgement, the Examiner seems to assert that because the rejection is made under 35 U.S.C. 103(a), such is not required. Yet the decision of the Federal Circuit and its concomitant requirements stated above apply to all obviousness determinations. Therefore, a motivation to make the combination must be found. Since none is present, no prima facie case of obviousness has been established.

Applicants respectfully disagree with the Examiner's assertion that Khirabadi discloses the use of both mannitol and lactose in compositions for the cryoprotection of cells (Office Action mailed 11/5/2003, p. 4). Khirabadi does not disclose mannitol and lactose in the same solution, nor even in separate solutions for the same purpose. Instead, Khirabadi discloses methods for vitrification of a blood vessel in a cryoprotectant solution (Col. 4, line 13). These solutions can contain a variety of nonpermeating cryoprotectants (Col. 6, line 27). Khirabadi

then provides merely a "laundry list" of nonpermeating cryoprotectants, one of which is lactose (Col. 6, line 41).

Khirabadi then discloses separate methods for removal of a blood vessel from vitrifiable concentrations of a cryoprotectant. (Col. 8, line 10-12). These methods can include the use of solutions containing low molecular weight osmotic buffering agents. Khirabadi then provides a "laundry list" of such agents, including mannitol (Col. 9, line 26). However, Khirabadi never discloses or suggests mannitol and lactose in the same solution, nor even in separate solutions used for the same purpose. Instead, the Examiner has combined these ingredients from two separate solutions useful for entirely opposing purposes. Therefore, no motivation is provided to combine mannitol and lactose in any solution based on the disclosure of Khirabadi. Furthermore, there is no use of polyvinyl alcohol by Khirabadi and therefore no motivation to use lactose and mannitol to ensure the full ice blocking activity of polyvinyl alcohol.

Therefore, there is no suggestion or motivation to make the asserted combination, and a prima facie case of obviousness has not been established. The combinations asserted above by the Examiner can be made only based on a hindsight reconstruction of the invention based on the Applicant's own disclosure. Such is not permitted under the patent laws. A determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. *ATD Corp. v. Lydall, Inc.* 159 F.3d 534; 48 USPQ2d 1321 (Fed. Cir. 1998). Instead, when a prior art reference requires selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself. MPEP 2145(X)(A); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132; 227 USPQ 543 (Fed. Cir. 1985). Since

Khiradadi provides no motivation to combine mannitol with lactose in a solution for the introduction and washout of vitrifiable concentrations of cryoprotectants in a cell, organ, or tissue, no prima facie case of obviousness has been made.

The Examiner also rejects claims 4, 7, 17, 20, and 27-29 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,194,137 (Khirabadi) in view of U.S. Patent No. 6,395,467 (Fahy et al.). This rejection is respectfully traversed.

Khirabadi has been discussed above. The claims included in this rejection further recite that the cryoprotectant is polyvinyl alcohol or a copolymer of vinyl alcohol and vinyl acetate. The rejection as phrased by the Examiner assumes that "the composition of US 6,194,137," is a carrier solution for the introduction and washout of vitrifiable concentrations of cryoprotectants comprising mannitol and lactose. But Khirabadi does not disclose any such composition, for the reasons stated above. Therefore, even the combination of these two references fails to establish a prima facie case of obviousness because the combination of Khirabadi and Fahy suffers from the same flaw. While the Fahy reference is acknowledged as a significant advance in the art, only the present invention teaches the inclusion of mannitol and lactose in solutions for the introduction and washout of vitrifiable concentrations of cryoprotectants.

The Examiner rejects claims 6-7, 18, 21, 27-19 under 35 U.S.C. 103(a) as allegedly being obvious over the combination of Khirabadi, Fahy, and Klebe. This rejection is respectfully traversed. Khirabadi and Fahy have been discussed above. This rejection has the same flaws as those already discussed. Khirabadi does not disclose a solution containing lactose and mannitol for reasons already stated above. Therefore, adding Fahy and Klebe to the rejection does not cure this flaw and the rejection does not meet the 3 requirements of obviousness as explained by the

Federal Circuit. Klebe merely provides a list of cryoprotective agents and does not provide any motivation to combine any of the listed compounds with mannitol or lactose. Therefore, no prima facie case of obviousness has been made. Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully submits that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date: April 5, 2004

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